Remarks

Claims 36-55 are pending. Claims 36, 47, and 48 were amended to specify one or more protrusions to maintain location or orientation of the seed. Support for the amendment is found at least in the figures, for example Figure 3; and page 35, lines 19-22.

Applicant believes that it is proper for the present amendment to be entered since it places the application in condition for allowance and does not require further search or consideration by the Examiner.

In the event this amendment and response does not result in a Notice of Allowance, the undersigned requests an interview with Examiner Samala, Examiner Vu, SPE Hartley, and a Quality Assurance Specialist (QAS).

Interview

The undersigned and Dr. Kaplan thank Examiner Samala and Examiner Vu for their time during the interview on December 11, 2008. During the interview, the prior art cited by Dr. Samala was discussed. The undersigned; the applicant, Dr. Kaplan; and Examiners Samala and Vu agreed that the references cited by the Examiner do not disclose or suggest seeds or strands containing protrusions which maintain location or orientation. While it is the position of the undersigned and Dr. Kaplan that the claims pending at the time of the interview are novel and non-obvious over the prior art, applicant has amended claim 36 to specify protrusions in order to facilitate allowance of the application. Applicant reserves the right to pursue broader claims and/or claims of a different scope in one or more continuation applications.

Rejection Under 35 U.S.C. § 103

Claims 36-55 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2001/0044567 to Zamora *et al.* ("Zamora") , in view of U.S. Patent Nos. 6,010,446 to Grimm ("Grimm") and 5,713,828 to Coniglione. Applicants respectfully traverse this rejection.

Legal Standard

The starting point for any obviousness analysis must be the Supreme Court's decision in *KSR,* which refocuses the determination of whether a claimed invention is obvious back to the process the Court had defined in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). There, the Court had held that the obviousness determination should address four factors, all of which must be considered, though not in any prescribed order: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need. *Id.* The Court cautioned that the fact finder should be careful about reading the teachings of the invention at issue into the prior art, to avoid applying inappropriate hindsight, *ex post* reasoning. *Id. at 36.*

Analysis

Zamora in view of Grimm and Coniglione

(1) The Scope and Content of the Prior Art

Zamora

Zamora describes a bioabsorbable brachytherapy device containing a tubular housing with sealed ends and an enclosed radioactive material (abstract). The radioactive

material includes a radioisotope, such as Pd-103 or I-125 (abstract). Specifically, Zamora discloses brachytherapy seeds made from a bioabsorbable polymer (paragraphs 32 and 58). Zamora discloses that the **outer surface** of the device has sufficient permanence or persistence so that the radioactive source material remains localized at the site of implantation (paragraph 0029). In other words, the outer surface of the device (i.e., the bioabsorbable polymer) remains intact long enough for the radioactive material to remain localized at the site of implantation.

Grimm

Grimm describes a spacer element for use between radioactive seeds that includes a center section and two cup-like end sections, the spacer member generally being cylindrical in exterior configuration (col. 1, line 65 to col. 2, line 10). The cup-like end sections are configured and arranged so as to provide a firm grip on the seeds (col. 2, lines 63-66). Grimm discloses that the interior surface of the cup-like portions can be roughened or ribbed, either completely or partially, to improve the gripping capability of the cup-like portions (col. 2, line 66 to col. 3, line 2). Grimm alleges that the presence of the spacer will prevent migration of the seeds (col. 3, lines 32-36).

Coniglione

Coniglione discloses a hollow-tube shape of the brachytherapy seed containing perforations, allegedly to minimize the chance of migration due to better attachment to tissue [abstract]. At Col. 5 lines 48-54, the specification states that this design "permits the growth of tissue into the device. This tissue growth acts to anchor the device at the application site and minimize the potential for migration." The perforations also allow the seed to be sutured in place to prevent migration.

(2) The Differences Between the Claimed Methods and the Prior Art

The Claimed Invention

Claim 36 defines a brachytherapy seed

A seed, for implantation into a subject, wherein the seed is a combination product comprising

a) a biocompatible carrier,

b) one or more therapeutic components,

c) an imaging, radiopaque, or other diagnostic marker, and

d) one or more protrusions to maintain location or orientation of the seed selected from the group consisting of one or more biodegradable structures effective to prevent migration of the seed into a target tissue, one or more biodegradable structures effective to maintain orientation in tissue, and one or more compliant setal structures which impart adhesive properties into a target tissue,

wherein the seed has a size and shape suitable for passing through the bore of a needle or catheter having an interior diameter of less than about 2.7 mm (10 gauge).

The Prior Art Fails to Disclose all of the Claimed Elements

None of Zamora or Grimm or Coniglione disclose

d) one or more protrusions to maintain location or orientation of the seed selected from the group consisting of one or more biodegradable structures effective to prevent migration of the seed into a target tissue, one or more biodegradable structures effective to maintain orientation in tissue, and one or more compliant setal structures which impart adhesive properties into a target tissue,

wherein the seed has a size and shape suitable for passing through the bore of a needle or catheter having an interior diameter of less than about 2.7 mm (10 gauge).

It is well established that 35 U.S.C. §103 requires a showing in the prior art of each claimed element, at a minimum, to create a *prima facie* case of obviousness.

Zamora does not disclose or suggest structures attached to the seed to maintain its position and/or orientation as required by the claims

The examiner has relied upon the statement in Zamora at paragraphs 29 and 31 referring to "the outer surface of device have sufficient permanence or persistence so that the radioactive source material remains localized at the site of implantation" for disclosure of protrusions for maintaining the location or orientation of the seed. This reliance is misplaced.

"Persistence" and "permanence" are not the same as protrusions for maintaining location or orientation of the seed. These terms are clearly used in reference to maintaining the integrity of the polymeric material used to manufacture the seed for a sufficient period of time for release of radiation, but not of the radionuclide itself, to occur at the site where the seed is implanted. There is no disclosure of any *structure* attached to the seed to maintain its location, let alone protrusions. Persistence is defined as (1) the act or fact of persisting, (2) the quality of being persistent, (3) continued existence or occurrence, or (4) the continuance of an effect after its cause is removed. Permanence is defined as the condition or quality of being permanent; perpetual or continued existence. Zamora discloses that the outer coating remains intact for a sufficient period of time for the radioactive material to remain localized. In other words, degradation of the bioabsorbable outer coating is sufficiently slow that the radioactive

source remains localized at the site of implantation. There is not disclosure or suggestion in Zamora to modify the seed to include structures which prevent migration or a change in position of the seed. In fact, Zamora discloses that the bioabsorbable material can be used to manufacture any of the seeds of Figures 1-6 (paragraph 0058). The structures in Figures 1-6 represent the seeds that were commercially available at the time Zamora was filed. All of the seeds shown in Figure 1-6 have a smooth surface; they do not contain a biodegradable structure that prevents migration as required by the claims.

The Examiner also alleges that Zamora discloses the use of biodegradable polymers, such as PLA and PLGA, that are the same as those claimed. Applicant respectfully disagrees. The pending claims are drawn to seeds requiring the following elements:

a) a biocompatible carrier,

b) one or more therapeutic components,

c) an imaging, radiopaque, or other diagnostic marker, and

d) one or more protrusions to maintain location or orientation of the seed.

The biocompatible carrier specified in claim 36 can be biodegradable, such as a biodegradable polymer (page 9, lines 9-26) or synthetic or natural biocompatible non-polymeric and/or inorganic materials (page 10, lines 1-3). The carrier is equivalent to the housing component in Zamora. The fact that there are materials in common is irrelevant. The claimed seeds require protrusions to maintain location or orientation of the seed. This can be accomplished a variety of ways including, but not limited to, modifying the seed to introduce structures which anchor the seed (*see* for examples Figures 3A, 3C, 3E, 3G, 3H, 3I, 8, and 9) or incorporating an adhesive material, such as polyimide hairs (page

34, line 15 to page 35, line 10). Zamora does not disclose or suggest modifying the seed to introduce one or more protrusions to maintaining the locations of the seed selected from the group consisting of one or more biodegradable structures effective to prevent migration of the seed into a target tissue, one or more biodegradable structures effective to maintain orientation in tissue, and one or more compliant setal structures which impart adhesive properties into a target tissue. Figures 1-6 in Zamora show prior art seeds; all of the seeds have a smooth surface, i.e., no protrusions to maintain position or orientation. Heintz *et al.*, *Med. Phys.*, Vol. 28, No. 4, 671-682 (2001), a copy of which is enclosed, was published shortly after the filing date of the application that issued as Zamora. Figure 1 on page 673 shows cross-sectional drawings of various seeds that were commercially available at, or were commercially available prior to, the time Zamora was filed. Again, all of the seeds have a smooth surface; none of the seeds have protrusions to maintain position or orientation.

Moreover, Zamora's abstract does not describe a degradable radiopaque marker as alleged by the Examiner. The reference at page 4 para 0051 is to platinum, tantalum, and bismuth, which are *not* biodegradable radiopaque markers, but rather high Z elements that, by definition, cannot be further metabolized or broken down.

Grimm and Coniglione do not cure the deficiencies of Zamora

Grimm

Grimm describes a spacer element for use between radioactive seeds that includes a center section and two cup-like end sections, the spacer member generally being cylindrical in exterior configuration (col. 1, line 65 to col. 2, line 10). The cup-like end sections are configured and arranged so as to provide a firm grip on the seeds (col. 2,

lines 63-66). Grimm discloses that the interior surface of the cup-like portions can be roughened or ribbed, either completely or partially, to improve the gripping capability of the cup-like portions (col. 2, line 66 to col. 3, line 2). Grimm alleges that the presence of the spacer will prevent migration of the seeds (col. 3, lines 32-36). However, Grimm does not disclose or suggest one or more biodegradable protrusions **on the seed itself**, effective to prevent migration of the seed into a target tissue, one or more biodegradable structures effective to maintain orientation in tissue, and one or more compliant setal structures which impart adhesive properties into a target tissue. In fact, Grimm clearly states that "seeds per se are not part of the present invention" (col. 2, line 34). Further, such spacers have no utility in single seed applications where the seeds are administered one at a time rather than in a strand. Grimm does not cure the deficiencies of Zamora.

Further, the spacers described in Grimm are not clinically useful. Grimm discloses that the length of the central portion of the spacer is 40-50 mm and the length of the cup-like end portions is 10-15 mm. Taking the minimum values, the total length of the spacer is at least 60 mm. This length is larger than the average diameter of the prostate, which is approximately 6 cm (*see* Leenstra *et al.*, *Int. J. Rad. Onc.*, Vol. 69, No. 3 (2007), a copy of which is enclosed, which discloses that 95% of prostates are less than 63 mm (6.3cm) in length). The treatment length of a strand should be correspondingly long. A strand have a 60-80 mm longer spacer, with a seed on each end would miss most of the prostate. The length of the spacer is clearly not therapeutically effective.

The Examiner acknowledges that Zamora and Grimm fail to disclose biodegradable structures to prevent migration or impart adhesive properties (*see* page 4, 3rd paragraph of the outstanding office action).

Coniglione

Coniglione discloses a **hollow-tube shape** of the brachytherapy seed, allegedly to minimize the chance of migration due to better attachment to tissue [abstract]. At Col 5 lines 48-54, the specification states that this design "permits the growth of tissue into the device. This tissue growth acts to anchor the device at the application site and minimize the potential for migration."

This is *not* one or more protrusions to prevent migration at the time of implantation as required by claim 36 and the claims dependent thereon. This is an alleged means to allow tissue growth, which allegedly then prevents migration. Not only is this clearly distinct from the claimed subject matter, but it contradicts all known interactions between brachytherapy seeds and tissue ingrowth. Implantation of seeds always results in radionecrosis of the tissue surrounding the seed. The tissue dies, without exception. The references cited below clearly demonstrate this phenomenon and the Examiner has provided no evidence to suggest otherwise.

- *Instantaneous tissue ingrowth is biologically implausible*

Seed stabilization must occur instantly because needle retraction is in large part responsible for dragging the seeds backwards down the needle track owing to suction. Instantaneous tissue ingrowth is biologically implausible and is not a realistic factor in prevention of seed migration.

- *Brachytherapy is used to prevent the regrowth of tissue*

Even if tissue ingrowth were important in preventing the migration of hollow-tube-shaped seeds, Conglione accurately teaches in the specification at Col 1, line 31 that

brachytherapy is used "*to prevent the regrowth of tissue.*" He further recites the obvious at Col 4 line 46; Col 8 line 23; and Col 12 line 31, that radioactive implants are meant to kill tissue. In view of these teachings, tissue ingrowth cannot reasonably be expected to factor into prevention of seed migration, even if the need for seed fixity were not instantaneous.

• *Even if a seed were not radioactive, one would not expect tissue ingrowth to occur*

In "Changes in the Tumor Microenvironment During Low-dose-rate Permanent Seed Implantation Iodine-125 Brachytherapy," Cron *et al* (IJROBP 63:4; 1245-51, 2005) described local tissue changes following implantation of both inactive and radioactive I-125 brachytherapy seeds. The seeds were manufactured by IBt (aka International Brachytherapy) Inc., Conglione's employer and the assignee of U.S. Patent No. 5,713,828. Fig. 7, page 1249, depicts a "kill zone" around both the inactive and radioactive seed implant regions at two days post implant. While no explanation for this phenomenon of non-radioactive seeds killing tissue is given, we learn that even if a seed were not radioactive, one would not expect tissue ingrowth to occur. [support for IBt supplying the seeds is found at page 1246, Materials & Methods, 3rd para]. A copy of this reference was filed with the amendment and response filed on May 16, 2008.

Ackerman, *Am. J. Roentg*, 114(3), 447-59 (1972) shows in Figures 3-5 a dead zone of tissue around the seed. A copy of this reference is enclosed.

Ostertag *et al.*, *Neurosurg*, 13(5) 523-528 (1983) shows in Figure 2 central calcified necrosis surrounding the seed. On page 525, paragraph 2, Ostertag states

"Because of the low photon energy of I-125, mush of the energy is absorbed by the tissue next to the implant. Accordingly we found an early and initially progressive tissue destruction around the implantation seed." A copy of this reference is enclosed.

Helpap, *World J. Urol.*, 20(4) 207-212 (2002) shows in Figure 2b that concentric fibrosis and fibrous vascular obliteration occurred in the vicinity of the implanted seeds. A copy of this reference is enclosed.

The references discussed above clearly show that implantation of radionuclide-containing seeds results in tissue death in the area around the seed. Thus, there is no tissue available to ingrow into the seed to anchor it into place as alleged by Coniglione. Further, perforating the seed can lead to leakage of the radionuclide if the seed is not adequately welded.

It is interesting to note that a commercially available seed of the type described in Coniglione, marketed as the InterSource^{125} seed or Optiseed (which replaced the InterSource seed), are no longer available and there are no plans to reintroduce the seeds to the market.

- *Hollow-tube-shape seeds migrate*

In "Prostate Postbrachytherapy Seed Distribution," Bloch *et al* (IJROBP 69:1; 70-78, 2007) describe using MRI and CT imaging to locate and quantify the extent of dislocated (page 76, 2nd para on right) and ectopic (page 76, top right para), *i.e.* migrated, hollow-tube-shape seeds from IBt. Page 71, Materials & Methods, para 1 states that Pd-103 seeds from IBt were assessed in the study. Migrated seeds were defined as those identified beyond the prostate, or "extraprostatic/periprostatic." Table 2, page 72, shows that 11.8±4.5% of 1,205 implanted seeds were identified as having migrated to an

extracapsular location. "The seeds were assigned to specific extraprostatic areas only if the dislocation was clearly visible: the seed was required to be completely extracapsular" (page 72, top right para). These findings prove that roughly 12% of hollow-tube-shape seeds migrate to outside of the prostate. Many more seeds would be expected to migrate to a lesser extent, remaining within the prostate but degrading the dosimetry outcome nonetheless. See for example the authors' comment on page 77, 3rd para left, where they state that it is often difficult to accurately determine the number of seeds implanted *"when these clump together."* Clumping occurs as a result of seed migration. A copy of this reference was submitted with the amendment and response filed on May 16, 2008.

Alternative, Coniglione discloses that the device can be anchored into place with a suture material or a surgical stainless steel wire or rod (abstract). The suture material, wire or rod can be threaded through the hollow tube (col. 4, lines, 49-65). Again there is not teaching or suggestion in Coniglione to incorporate protrusions onto the surface of the seed or strand to maintain position or orientation as required by claim 36 and the claims dependent thereon. The figures in Coniglione show only smooth seeds; there are no protrusions on the surface. In fact, International Brachytherapy S.A. ("IBt"), the assignee of the '828 patent, received a warning letter from the FDA in January 2002, in which the FDA objected to the company's promotional materials for their product InterStrand. Specifically, the FDA objected to claims by the company that InterStrand technology eliminates seed migration and will not jam. The FDA asserted that such statements are misleading as the labeling for the product clearly states that the seeds are held in place by the monofilament suture and that it is the sutures that minimize seed movement or migration. Further, the FDA argued that no data was ever submitted by IBt

to indicate that the InterStrand eliminates seed migration. A copy of an excerpt from Warning Letter Bulletins, July 28, 2003, describing the contents of the warning letter, is enclosed.

The references in combination teach away from the claimed composition

As discussed above, the references alone or in combination do not disclose each and every element of the claims. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. However, even if one could argue that such a case has been established, the references clearly teach away from the claimed methods.

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *In re Caldwell*, 50 C.C.P.A. 1464, 319 F.2d 254, 256, 138 U.S.P.Q. (BNA) 243, 245 (CCPA 1963) (reference teaches away if it leaves the impression that the product would not have the property sought by the applicant).

Zamora does not disclose or suggest any protrusions for preventing migration and/or rotation of seeds. As discussed above, the seeds described in Zamora are cylindrical-shaped seeds, wherein the outer surface is formed of a bioabsorbable polymer, wherein the outer surface is smooth and featureless. Zamora does not disclose or suggest biodegradable structures on the surface of the seed that prevent migration and/or rotation. Grimm alleges that migration can be reduced by using the spacers described therein.

Coniglione alleges that migration can be reduced by introducing perforations into the seed to allow for tissue ingrowth.

One of ordinary skill in the art, reading Grimm, Zamora, and Coniglione, would be motivated to develop a spacer which prohibits migration in combination with a perforated seed that allowed for tissue ingrowth to anchor the seed, not the compositions developed by the Applicant. One or ordinary skill in the art, reading Zamora, Grimm, and Coniglione, would take a path divergent from the path taken by the application. Accordingly, the references cited by the Examiner clearly teach away from the claimed compositions.

The limitation "one or more means to maintain location or orientation of the seed" is not overly broad

The Examiner alleges that the phrase "one or more means to maintain location or orientation of the seed" is overly broad. Application respectfully disagrees. However, in order to facilitate prosecution, claim 36 has been amended to specify one or more protrusions. The specification discloses several examples of these protrusions, for example, in the figures (*see* Figure 3, Figure 6, Figure 8, and Figure 9) as well as page 34, line 15 to page 35, line 10 and page 37, line 19 to page 39, line 7).

The Examiner also alleges that suitable brachytherapy seeds for implantation into the tumerous tissues are well known in the art and that known fabrication methods and techniques permit the construction of brachytherapy seeds having a variety of forms or shapes or otherwise minimize the chance of migration. However, the Examiner has provided no evidence to support this statement. In fact, the Examiner concedes that Zamora and Grimm do not disclose or suggest the structures specified in claim 36.

Further, as discussed above, the Examiner has misconstrued the teachings of Coniglione. Coniglione discloses structures which allow tissue ingrowth to anchor the structure, not seeds having protrusions to maintain location or orientation at the time of implantation. Therefore, the Examiner has failed to show that one of ordinary skill in the art would be motivated to combine and/or modify Zamora, Grimm, and Coniglione to arrive at the claimed compositions.

Evidence of Secondary Indicia of Non-obviousness

Even if the examiner had found separate references identifying the claimed elements, applicant has evidence of the type deemed by the U.S. Supreme Court sufficient to rebut an allegation of obviousness: long standing need and commercial success.

Long Standing Need

The problem with migration is a significant, and to date, unsolved problem in the field. See any of the following references.

In "A Case of Strand Migration after Prostate Seed Implant," Chuba *et al* (Poster, ESTRO 2006) demonstrated that "both individual seeds and entire strands may migrate when using strand technique." A copy of this reference was submitted with the amendment and response filed on May 16, 2008.

In "Comparison of Day 0 and Day 14 Dosimetry for Permanent Prostate Implants Using Stranded Seeds," McLaughlin *et al* (IJROBP 64:1; 144-50, 2006) noted that in their study of 28 patients, "The findings of this study have clearly demonstrated a substantial change in seed position relative to the prostate and independent of prostate volume changes" (page 149, last para left). "The most common pattern was a shift of the

prostate superiorly relative to the seeds, resulting in decreased prostate coverage." (page 148, 3rd para left). A copy of this reference was submitted with the amendment and response filed on May 16, 2008.

In "PSA Recurrence after Brachytherapy for Seed Misplacement," Gacci *et al* (Prostate Cancer Prostatic Dis 2007 Oct, 1-3) reported that strand migration from a portion of a patient's prostate "was the main cause of tumor relapse in this area" (page 2, 1st para right)." "...In the present case, PSA recurrence occurred for seeds misplacement after a correct primary seeds positioning [*sic*]." (page 3, top left). A copy of this reference was submitted with the amendment and response filed on May 16, 2008.

In "Evaluation of Source Displacement and Dose-volume Changes after Permanent Prostate Brachytherapy with Stranded Seeds," Pinkawa *et al* (Radiother Oncol 84; 190-6, 2007) found that "apparently, longer strands are moving more easily along the prior needle track, while single seeds or shorter strands are more likely to tilt in the prostate." (page 194, top right para). A copy of this reference was submitted with the amendment and response filed on May 16, 2008.

Mick Applicator users comprise about half the population of clinicians doing brachytherapy. *See* "Migration of Implanted Free Radioactive Seeds for Adenocarcinoma of the Prostate Using a Mick Applicator," Kunos *et al*, Brachytherapy 3; 71-77, 2004. Kunos describes seed migration occurring in 42% of patients (page 72, last para right). A copy of this reference was submitted with the amendment and response filed on May 16, 2008.

Chen *et al*. "Th-B-224C-01: Permanent Prostate Brachytherapy Using Plastic Palladium-103 Seeds", *Med. Phys.*, 33, 2264 (2006) discloses that three seeds migrated to

the lungs (line 5 in results) and that with respect to dosimetry and implant processes, there are no differences between plastic and metallic seeds. Chen suggests that there are no discernible differences between plastic (e.g., polymeric seeds) and metallic seeds with respect to migration, and that replacing metallic seeds with polymeric seeds alone does not overcome the problems associated with migration. A copy of this reference is enclosed.

Applicant has shown that up to the present time, seed migration is still a significant problem, particularly in brachytherapy, and that the prior art seeds have failed to solve the problem of seed migration.

Commercial Success

The enclosed materials relate to the recent introduction of brachytherapy seeds that have protrusions for maintaining their location. This evidence, not supported by an expensive ad campaign or big name speakers, merely by the long felt need for such devices and the success immediately observed by those in the field, overwhelming demonstrates the non-obviousness of the claimed subject matter. The Anchorseed went on sale in March 2008. There has generally been a steady increase in the number of patients treated with Anchoseed, with 57 treated in October 2008. Through October 2008, approximately 300 patients have been treated. Assuming 80 seeds are used per patient, that is approximately 24,000 seeds that have been implanted through October 2008. At approximately $30.00/seed, sales of approximately $0.72 million have been achieved through October 2008. Sales are expected to exceed $1 million by January 2009. A bar graph showing sales from March 2008 through October 2008 is enclosed.

Comparison of Anchorseed to the prior art

A video describing the Anchorseed product is available at www.anchorseed.com/video. This video was shown to Examiners Samala and Vu during the interview on December 11, 2008. Anchorseed contains four rings around the circumference of the seed, one at each end cap of the seed and two smaller medial rings. The rings are connected by two longitudinal ribs that run opposite each other along the lateral surface of the seed and connect the two end rings. The biodegradable elements are made from polyglycolic acid (PGA). The incorporation of the rings and the rib results in a seed having a diameter 30% greater than standard seeds. The larger seed dimensions fill the needle track more completely than standard seeds, thereby minimizing draw back when administered into the tissue. Drawback is frequent adverse event associated with standard seeds.

Dr. Thomas Shanahan, who describes his experience with the Anchorseed in the video, states that Anchorseed does not slip along the needle track, a phenomenon often observed with standard seeds, and that the seeds remain where they are administered with little or no migration. Dr. Shanahan also stated that the suction effect associated with the administration of brachytherapy seeds can be mitigated using the Anchorseed, which minimizes time in the operating room. Finally, Anchorseed can be used with a standard Mick applicator, avoiding the need for specialized equipment for administration.

The video footage showing administration of the Anchorseed demonstrates that the seed remains parallel to the needle track upon deployment, without any wake or shift of the seed as the needle is withdrawn and deployed to the next location. Further, the suction or pressure effect often observed with the Mick application has been minimized

through the design of the Anchorseed. Fluoroscopy of the plain pelvis at day 14 shows reproducibility of the location and orientation of the seeds compared to day 0.

Heintz *et al.*, cited above, compares I-125 sources for permanent interstitial implants. Figure 1 on page 673 shows cross-sectional drawings of different sources with a rod, wire, or cylinder core design, including International Brachytherapy, Inc.'s InterSource^{125} seed, which is a tubular metallic seed. This seed is described in Coniglione. The InterSource^{125} seed is no longer sold. Optiseed, the plastic replacement for the InterSource Pd-103 seed, is also no longer available. It is important to note that all of the seeds shown in Figure 1 have a smooth surface, lacking any structures or features which prevent migration as required by the claims. These are the types of seeds referred to by Dr. Shanahan in the video described above. The seeds shown in Figure 1 are all of the commercially available embodiments. There are no others.

Summary

The claimed seeds are novel and non-obvious. The advance provided by the means for securing the seeds solves a long standing problem and has been recognized by the industry in an immediate and significant manner as providing such a solution. The claimed seeds offer a means of enhancing seed and strand fixity such that implant dosimetry is improved, irrespective of the implant technique. It also may eliminate the logistical nightmare entailed in stranding your own seeds.

Double Patenting Rejection

Claims 36-40, 45, and 47-55 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 10, 12, 15, 30, 32, 35, and 36 of U.S. Patent No. 6,746,661 to Kaplan. This rejection is traversed.

The mere fact that claims are drawn to brachytherapy seeds, formed of a biodegradable polymer, but having distinct limitations - one drawn to elastic properties of the polymer and the other to distinct structures for maintaining the location of the seed, does not make them obvious over the other. If they had appeared in the same application, the examiner would have issued a restriction requirement on the grounds that they required different searches, in different arts. Elastic polymers do not make obvious protrusions for maintaining seeds in a particular location.

The Examiner alleges that the polymers used in the instant claims and the polymers disclosed in U.S. 6,746,661 are biodegradable polymers and would have elastic properties. This statement is unclear. There is no relationship between biodegradability and elasticity. For Example, poly-3-hydroxybutyrate (PHB) and polylactic acid (PLA) are biodegradable polymers, however, are typically classified as stiff and brittle.

The Examiner also alleges that since the claims in the '661 patent are silent regarding the migration of seeds from the implantation site, the present claims are within the scope of the '661 claims. This is not the correct legal standard for double patenting.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is - does any claim in the application define an invention that is anticipated by, or is merely an obvious variation of, an invention claimed in the patent? If the answer is yes, then an "obviousness-type" nonstatutory double patenting rejection may be appropriate. Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent. See *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 58 USPQ2d 1869 (Fed. Cir. 2001); *Ex parte Davis*, 56 USPQ2d 1434, 1435-36 (Bd. Pat. App. & Inter. 2000).

A double patenting rejection of the obviousness-type, if not based on an anticipation rationale, is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, the analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Since the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection, the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are employed when making an obvious-type double patenting analysis. These factual inquiries are summarized as follows:

(A) Determine the scope and content of a patent claim relative to a claim in the application at issue;

(B) Determine the differences between the scope and content of the patent claim as determined in (A) and the claim in the application at issue;

(C) Determine the level of ordinary skill in the pertinent art; and

(D) Evaluate any objective indicia of nonobviousness.

The conclusion of obviousness-type double patenting is made in light of these factual determinations.

Any obviousness-type double patenting rejection should make clear:

(A) The differences between the inventions defined by the conflicting claims - a claim in the patent compared to a claim in the application; and

(B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the patent.

When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle GmbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992).

The Examiner has failed to do the analysis described above. The claims of the '661 patent describe a brachytherapy seed comprising a plurality of microspheres comprising a biocompatible component, one or more therapeutic active agents, and a radiopaque marker, wherein the seed has a size and shape suitable for passing through the

bore of a needle having an interior diameter of less than 2.7 mm. In contrast, the pending claims do not require a plurality of microspheres and further require one or more protrusions of maintaining the location or orientation of the seed. The claims of the '661 patent do not disclose or suggest one or more protrusions for maintaining the location or orientation of the seed. Accordingly, claims 36-40, 45, and 47-55 are not obvious over the claims in U.S. Patent No. 6,747,661 to Kaplan, et al.

Allowance of claims 36-55, as amended, is respectfully solicited.

Respectfully submitted,

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